UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,845	10/18/2001	Samy Ashkar	CMCC 779	7069

23579 7590 08/08/2005

PATREA L. PABST
PABST PATENT GROUP LLP
400 COLONY SQUARE
SUITE 1200
ATLANTA, GA 30361

EXAMINER	
DEBERRY, REGINA M	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 08/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/981,845	ASHKAR ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5 and 6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 15 June 2005 has been entered in full. Claim 4 is cancelled.

The Examiner acknowledges that cancellation of non-elected species claim 1 (elected species SEQ ID NO:11) is not, as yet, required.

Claims 1-3, 5 and 6 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejection to claims 1-6 under 35 U.S.C. 102(b) as being anticipated by Young *et al.*, Genomics, 1990, as set forth at page 6 of the previous Office Action (17 March 2005) is *withdrawn*.

Claim Rejections - 35 USC § 112, First Paragraph

Claims 1-3, 5-6 remain rejected under 35 U.S.C. 112, first paragraph, scope of enablement, while being enabling for:

an active osteopontin peptide fragment comprising the amino acid of SEQ ID NO:11 wherein the peptide increases cell attachment of *osteoprogenitor cells* to a material and increases cell spread of *osteoprogenitor cells,*

does not reasonably provide enablement for:

an active osteopontin peptide fragment comprising the amino acid of SEQ ID NO:11 which binds *any integrin receptor* on the surface on *any cell type*.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The basis for this rejection is set forth at pages 3-5 of the previous Office Action (17 March 2005).

Applicant states that both SEQ ID NO:11 and SEQ ID NO:15 have conserved domains similar to osteopontin, which binds to a number of integrins, including, $\alpha_v\beta_3$. Applicant cites a Blast 2 Sequence comparison and Hu *et al.* (reference of record). Applicant maintains that although the specification uses osteoprogenitor cells as an example, osteopontin-derived peptides of this invention would be able to interact with integrins found on diverse cell types, such as those recited in claim 6. Applicant submits Horton (Biochem. Cell Biol., 1997).

Applicant's arguments have been fully considered but are not deemed persuasive. Hu *et al.* teach that **osteopontin, not SEQ ID NO:11 or SEQ ID NO:15, only binds to integrins $\alpha_v\beta_3$, $\alpha_v\beta_1$ and $\alpha_v\beta_5$, not all of the integrins as recited in instant claim 5** (Emphasis added). Horton states, "the site of highest expression of $\alpha_v\beta_3$, *in vivo*, is the osteoclast". "Lower levels are also seen in platelets, megakaryocytes, kidney, some vascular smooth muscle, endothelium and placenta". **Horton does not teach the presence of $\alpha_v\beta_3$ integrins in stem or precursor cells, as recited in instant claim 6** (Emphasis added). Most importantly, the purported utility

of the instant application is the successful osseointegration of an implant into the surrounding tissues. The specification teaches that the primary challenges faced in the fabrication of new endosseous implants are to increase the rate of osseointegration and the percentage of bone apposition. The instant claims encompass a number of diverse types of cells. The instant specification fails to teach that these various cell types have osseointegration activity. Only osteoprogenitor cells have been shown to have osseointegration activity.

Applicant states that the Examiner alleges that SEQ ID NO: 15 or any other fragment of osteopontin will not bind to CD44 and $\alpha_v\beta_1$ because osteoprogenitor cells were able to attach and spread in the presence of antibodies against CD44 and $\alpha_v\beta_1$. Applicant asserts that one cannot come to that conclusion from the data presented, because the assay described in the specification is not a binding assay. Applicant maintains that all one can deduce is that CD44 and $\alpha_v\beta_1$ are either weakly expressed or not expressed by osteoprogenitor cells and/or osteopontin-fragment induced cell migration and cell spread in osteoprogenitor cells preferentially occurs through an integrin (i.e. $\alpha_v\beta_3$) or integrins other than CD44 and $\alpha_v\beta_1$. Applicant cites Noonan *et al.* (reference of record) which describes reduced expression of CD44 in osteoprogenitor cells.

Applicant's arguments have been fully considered but are not deemed persuasive. The instant specification states, "Table 8 also illustrates that antibodies to different integrins may be used to block **binding** to specific integrins". Contrary to Applicant's assertion, Table 8 employs binding assays to discern integrin binding

specificity. Please see page 53, lines 17-21 for clarification. Table 8 illustrates that human osteoprogenitor cells will attach and spread to surfaces coated with SEQ ID NOs:9-15 (page 53, line 22-page 54, line 2). Antibodies to different integrins were used to block binding of osteoprogenitor cells to the coated surfaces. Only antibodies made against $\alpha_v\beta_3$ integrin were able to significantly diminish osteoprogenitor cells from binding to surfaces coated with SEQ ID NO:15 (mOC-1016)(page 53, lines 17-21 and page 54). This means that SEQ ID NO:15 binds osteoprogenitor cells through the $\alpha_v\beta_3$ integrin receptor. Osteoprogenitor cells were able to attach and spread on plates coated with SEQ ID NO:15 in the presence of antibodies against CD44 and $\alpha\beta1$ (page 54).

As was stated above, the purported utility of the instant application is the successful osseointegration of an implant into the surrounding tissues. Thus implants coated with these peptides should bind macromolecules supportive of osteoblast function in order to make a good bone implant. Table 8 demonstrates an 87% and 89% spread of osteoprogenitor cells in the presence of anti-CD44 and anti-$\alpha\beta1$ antibodies, respectively, compared to only a 12% spread in the presence of anti-$\alpha_v\beta_3$ antibodies. Please see page 54 (compare 4th column, lines 22 and 27 with line 18). The data suggest that SEQ ID NO:15 does not bind integrin receptors CD44 or $\alpha\beta1$ in osteoprogenitor cells. The Examiner agrees with Applicant that the data could also suggest that osteoprogenitor cells do not express CD44 and $\alpha\beta1$ integrins at all or expresses it at very low levels. However, as was stated above, the peptides should bind macromolecules supportive of osteoblast function in order to make a good bone implant. Table 8 suggests that SEQ ID NO:15 does not bind CD44 or $\alpha\beta1$ in a way,

which is supportive of osteoblast function. Furthermore, instant claim 5 recites other integrins, which have not been tested. There is no predictability as to which integrin receptor would bind surfaces coated with the instant peptides because the specification discloses that only anti-$\alpha_v\beta_3$ antibodies inhibited osteoprogenitor cells from spreading to plates coated with SEQ ID NO:15.

Lastly, Applicant discusses Tuck *et al.* (reference of record). Applicant states that Tuck shows that migration of two cells lines, 21PT and 21NT is blocked with antibodies against $\alpha_v\beta_5$ and $\beta1$ integrin, but not with antibodies against $\alpha_v\beta_3$, while the migration of the third cell line, MDA-MB-435 is blocked with antibodies against $\alpha_v\beta_3$. Applicant asserts that if one uses the Examiner's reasoning to analyze the results of 21PT and 21NT cell lines, one would come to the erroneous conclusion that osteopontin does not bind $\alpha_v\beta_3$, when it is well known in the literature that osteopontin binds this integrin. Applicant cites case law.

Applicant's arguments have been fully considered but are not deemed persuasive. Applicant is comparing mammary epithelial cell lines to osteoprogenitor cells (cell type actually employed in the specification). The Examiner stated that "osteoprogenitor cells attach and spread to surfaces coated with SEQ ID NOs:9-15 and only antibodies to $\alpha_v\beta_3$ integrin significantly diminish SEQ ID NO:15 from binding". "This means that SEQ ID NO:15 binds the $\alpha_v\beta_3$ integrin receptor". "However, this is not tantamount to SEQ ID NO:11 (or any other osteopontin-derived peptide) binding **any integrin on any cell type**". "This is demonstrated by the fact that SEQ ID NO:15 was able to cause osteoprogenitor cells to attach and spread in the presence of antibodies

against CD44 and αβ1". "This means that SEQ ID NO:15 does not bind integrin receptors CD44 and αβ1". "Thus not all osteopontin-derived peptide fragments can bind any type of integrin receptor". Please see previous Office Action (17 March 2005, page 5, last paragraph).

The Examiner was making the point that osteopontin-derived peptide fragments can not bind any type of integrin receptor on any type of cell. Applicant has demonstrated this point with the Tuck reference. The mammary epithelial cell lines employed by Tuck *et al.,* express different integrin receptors. Osteopontin does not bind $\alpha_v\beta_3$ in the 21PT and 21NT cell lines but it does bind $\alpha_v\beta_3$ in the MDA-MB-435 cell line. It would require an indeterminate quantity of unpredictable investigational experimentation of the skilled artisan to determine which cell type expressed which integrin receptor, then discern if that cell type expressing that specific integrin receptor bound surfaces coated with the various peptides. Without sufficient guidance, the amount of experimentation would be undue for one skilled in this art.

The instant claims recite a genus of various cell types and integrins but the specification only discloses a species. The disclosure fails to make and/or use a representative number of species to enable the recited genus. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
7/25/05

JOSEPH MURPHY
PATENT EXAMINER